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*Published in:*

International Journal of Radiation Oncology, Biology, Physics

*DOI:*

[10.1016/j.ijrobp.2016.12.008](https://doi.org/10.1016/j.ijrobp.2016.12.008)

*Publication date:*

2017

*Document version*

Publisher's PDF, also known as Version of record

*Document license:*

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*Citation for published version (APA):*

Stick, L. B., Yu, J., Maraldo, M. V., Aznar, M. C., Pedersen, A. N., Bentzen, S. M., & Vogelius, I. R. (2017). Joint Estimation of Cardiac Toxicity and Recurrence Risks After Comprehensive Nodal Photon Versus Proton Therapy for Breast Cancer. *International Journal of Radiation Oncology, Biology, Physics*, 97(4), 754-761. <https://doi.org/10.1016/j.ijrobp.2016.12.008>

Clinical Investigation

# Joint Estimation of Cardiac Toxicity and Recurrence Risks After Comprehensive Nodal Photon Versus Proton Therapy for Breast Cancer



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Received Sep 22, 2016, and in revised form Nov 22, 2016. Accepted for publication Dec 2, 2016.

## Summary

Evidence-based bioeffect models were used to provide patient-level risk estimates for clinically delivered photon therapy plans compared with proton therapy plans in 41 consecutive patients with left-sided breast cancer referred for comprehensive nodal irradiation. The joint estimation of risk of recurrence caused by target dose compromises and risk of cardiac morbidity

**Purpose:** The study aims to perform joint estimation of the risk of recurrence caused by inadequate radiation dose coverage of lymph node targets and the risk of cardiac toxicity caused by radiation exposure to the heart. Delivered photon plans are compared with realistic proton plans, thereby providing evidence-based estimates of the heterogeneity of treatment effects in consecutive cases for the 2 radiation treatment modalities.

**Methods and Materials:** Forty-one patients referred for postlumpectomy comprehensive nodal photon irradiation for left-sided breast cancer were included. Comparative proton plans were optimized by a spot scanning technique with single-field optimization from 2 en face beams. Cardiotoxicity risk was estimated with the model of Darby et al, and risk of recurrence following a compromise of lymph node coverage was estimated by a linear dose-response model fitted to the recurrence data from the recently published EORTC (European Organisation for Research and Treatment of Cancer) 22922/10925 and NCIC-CTG (National Cancer Institute of Canada Clinical Trials Group) MA.20 randomized controlled trials.

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This study was supported by Danish Cancer Society grant R125-A7989-15-S37, Kirsten and Freddy Johansen's Foundation, Cancer Research UK grant C8225/A21133, and National Institutes of Health grant P30 CA 134274-04.

Conflict of interest: I.R.V. and M.C.A. receive grants and educational fees from Varian Medical Systems.

Supplementary material for this article can be found at [www.redjournal.org](http://www.redjournal.org).

**Acknowledgments**—The authors acknowledge Birgitte Offersen and Lise Thorsen for supplying reanalysis of the Danish Breast Cancer Cooperative Group Internal Mammary Node study with the endpoint of disease-free survival for sensitivity analysis of our model with respect to using data from the randomized studies versus the Danish Breast Cancer Cooperative Group study.

differed markedly between patients and radiation treatment modalities.

**Results:** Excess absolute risk of cardiac morbidity was small with photon therapy at an attained age of 80 years, with median values of 1.0% (range, 0.2%-2.9%) and 0.5% (range, 0.03%-1.0%) with and without cardiac risk factors, respectively, but even lower with proton therapy (0.13% [range, 0.02%-0.5%] and 0.06% [range, 0.004%-0.3%], respectively). The median estimated excess absolute risk of breast cancer recurrence after 10 years was 0.10% (range, 0.0%-0.9%) with photons and 0.02% (range, 0.0%-0.07%) with protons. The association between age of the patient and benefit from proton therapy was weak, almost non-existing (Spearman rank correlations of  $-0.15$  and  $-0.30$  with and without cardiac risk factors, respectively).

**Conclusions:** Modern photon therapy yields limited risk of cardiac toxicity in most patients, but proton therapy can reduce the predicted risk of cardiac toxicity by up to 2.9% and the risk of breast cancer recurrence by 0.9% in individual patients. Predicted benefit correlates weakly with age. Combined assessment of the risk from cardiac exposure and inadequate target coverage is desirable for rational consideration of competing photon and proton therapy plans. © 2016 Published by Elsevier Inc.

## Introduction

Recent randomized controlled trials have demonstrated a clinically relevant benefit of lymph node irradiation in breast cancer patients with certain adverse factors (1, 2), consistent with nonrandomized evidence from a population-based study (3). Irradiation of the internal mammary nodes (IMNs) in left-sided breast cancer patients will, however, inevitably increase the radiation exposure to the cardiac structures, which has been shown to increase the risk of cardiac morbidity and death (4). Current practice most often compromises target coverage if necessary to adhere to cardiac dose constraints defined in treatment guidelines. The application of advanced photon therapy techniques can improve the target coverage-cardiac dose balance (5-7) as compared with historical techniques, but compromises are still inevitable. In this study, joint radiobiological modeling of cardiotoxicity and tumor recurrence risks is applied to quantify the patient-specific risk estimation. Clinically delivered photon dose plans are compared with proton plans to estimate the patient-level outcomes after the 2 radiation treatment modalities.

The marked heterogeneity in cardiac exposure in patients undergoing comprehensive breast cancer irradiation is a consequence of anatomic differences. This study included all 41 patients referred to our standard protocol for left-sided postlumpectomy radiation therapy with comprehensive nodal irradiation in 2015. This approach allows assessment of the variation in potential patient benefit from referral to proton therapy.

## Methods and Materials

Forty-one patients referred to Rigshospitalet during 2015 for unilateral left-sided postlumpectomy locoregional radiation therapy including the ipsilateral IMN chain were included in the study. The planning computed tomography (CT) scan from the clinically delivered photon therapy was

used for developing a competing proton beam spot scanning plan. All patients were scanned in the supine position with the deep inspiration breath-hold (DIBH) technique according to department guidelines (8).

Original target structure delineations for the delivered photon plans were used in this study: The whole breast with retraction from the skin of 5 mm and lymph nodes (IMN, level II axillary, level III axillary, level IV, and interpectoral) were delineated as clinical target volumes (CTVs) according to guidelines from the European Society for Radiotherapy and Oncology (ESTRO) (9). Level I was irradiated in 1 patient and dissected in all others.

The heart had generally not been delineated for the delivered plans (with few exceptions) following the 2015 standard procedure at Rigshospitalet, which limited dose to the left anterior descending coronary artery (LADCA) as a dose metric related to cardiac risk. Thus the whole heart was contoured or recontoured retrospectively for the purpose of this study following published guidelines (10). All other contours were delineated by the treating physician at the time of treatment (ie, multiple observers).

The prescribed dose was 50 Gy in 25 fractions for all patients. For patients younger than 50 years, a boost was delivered, but this was not considered for the purpose of this study (contributed  $<0.2$  Gy to mean heart dose [MHD] for all patients).

## Photon planning

Thirty-nine patients were treated with 3-dimensional (3D) conformal radiation therapy (CRT) comprising 2 main tangential opposing breast fields and a supraclavicular field (or fields) with the beam junction at the isocenter and 6 to 11 forward planned supplementary fields (examples of beam configurations are shown in Fig. A1; available online at [www.redjournal.org](http://www.redjournal.org)). Six megavolts was used for most fields, sometimes supplemented by 18 megavolts to reach deep-seated targets or reduce hot spots. Planning target volumes (PTVs) were not used for the 3D CRT plans;

however, a CTV-to-field border distance of 10 mm was applied above the isocenter. When target coverage compromises were required, CTV delineation was not modified; instead, a help structure was defined or a controlled compromise on CTV coverage was performed.

The remaining 2 patients were treated with hybrid plans: volumetric modulated arc therapy combined with 3D CRT (11). Both these patients had the heart delineated and prioritized in addition to the LADCA. A volumetric modulated arc therapy-specific PTV was created for optimization by a 5 to 6 mm expansion of the CTV and contracted to 3 to 4 mm below the skin surface. Eclipse, version 13.0 (Varian Medical Systems), with the AAA algorithm (29 patients) or the AcurosXB algorithm (12 patients), was used for dose calculation.

Four patients underwent rescanning or replanning during the radiation therapy course. For these cases, the plan used for the majority of fractions was chosen as the photon reference for the comparison.

Clinical planning objectives were to cover the whole breast CTV by between 95% and 107% of the prescribed dose and the lymph node CTVs with 90% to 107% of the dose. The maximum dose to the LADCA was <20 Gy, and the left lung  $V_{20\text{Gy}}$  (ie, volume that receives  $\geq 20$  Gy) was  $\leq 35\%$ . No part of the body should receive >110% of the prescription dose.

## Proton planning

Proton plans were optimized in Eclipse, version 13.6, and the plans were approved as suitable for clinical treatment delivery by the physicians and physicists. A proton beam-specific PTV was created for optimization. The breast PTV was created with a lateral margin of 5 mm to account for setup errors, as well as a distal margin of 2 to 4 mm to account for range uncertainties, and it excluded the chest wall, ribs, and intercostal muscle posteriorly and 3 to 4 mm of skin anteriorly. The lymph node PTV was created with a 5 mm isotropic margin without any contractions. Special PTVs with a distal margin of 10 mm were created for 2 patients with breast implants (the implants were not a part of the breast CTVs). The proton plans were planned on a nonclinical system but assuming the monitor units to be defined as relative biological effectiveness-corrected doses (ie,  $1.1 \times$  physical dose).

Two en face beams were used: one field with angles in the range from  $5^\circ$  to  $10^\circ$  and the other in the range from  $50^\circ$  to  $60^\circ$  (Fig. A1; available online at [www.redjournal.org](http://www.redjournal.org)). Plans were optimized with single-field optimization in which each beam is optimized independently to cover the target uniformly to 50% of the prescribed dose. A range shifter of water-equivalent thickness of 57 mm was applied. The spot spacing was fixed at 0.5 mm. The proton plans were normalized to a mean total CTV dose of 50 Gy.

In 3 cases the CT scans included air cavities. The density of the air cavities was assigned to be water by overriding the

Hounsfield units for planning purposes to ensure adequate proton energy to deliver the prescribed dose in case the air cavities were filled with fluid. The planning objectives were to cover the total CTV by between 95% and 107% of the prescribed dose while dose to heart, LADCA, and lung should be as low as reasonably achievable.

## Robustness analysis

Uncertainties in patient setup and proton beam range were estimated by the integrated plan robustness tool in Eclipse. Isocenter shifts were assumed to have a normal distribution in each fraction, with  $1.96 \times \text{SD} = \pm 5$  mm in the x, y, and z directions and constant calibration errors of  $1.96 \times \text{SD} = \pm 3.5\%$ . Appendix (available online at [www.redjournal.org](http://www.redjournal.org)) presents details of the robustness analysis. A corresponding robustness analysis of the photon plans toward setup uncertainties was performed as described in Appendix (available online at [www.redjournal.org](http://www.redjournal.org)).

## Plan evaluation and bioeffect modeling

A homogeneity index (HI) (12) was applied to evaluate CTV coverage:  $\text{HI} = (\text{D2} - \text{D98})/\text{D50}$ , where D2, D50, and D98 are the doses received by 2%, 50%, and 98% of the CTV, respectively. A low HI implies homogeneous coverage.

Table S13 in the appendix of the article by Darby et al (4) contains excess absolute risk (EAR) estimates of at least 1 acute coronary event (ACE) at age 80 years, where an ACE was defined as myocardial infarction, coronary revascularization, angina, or death from ischemic heart disease. For the purpose of this study, we used bivariate polynomial interpolation between table values (poly55; MatLab, The MathWorks) with the MHDs from the photon or proton plan and the patient's actual age at the time of treatment as the input variables; all patient cases were modeled both with and without pre-existing cardiac risk factors (CRFs). For 4 patients aged 26, 31, 35, and 36 years, the model input age was set to 40 years because of the range of the original tables.

The EAR of breast cancer recurrence 10 years after treatment as a consequence of target dose compromises was modeled as follows: Clinical effect size was derived from the empirical hazard ratio (HR) for disease-free survival (DFS) from the meta-analysis of the EORTC (European Organisation for Research and Treatment of Cancer) 22922/10925 and NCIC-CTG (National Cancer Institute of Canada Clinical Trials Group) MA.20 trials (1, 2). The meta-analysis yields  $\text{HR} = 0.86$  (13) when adding nodal irradiation to primary target irradiation. A linear dose-response model was assumed for the benefit of the proportion of the mean dose to IMN. For example, if the mean IMN dose was 35 Gy instead of 50 Gy (prescribed dose) in a given patient, this patient was expected to receive 70% of the benefit seen in the randomized trials (effective hazard

ratio  $[HReffective] = 1 - 0.14 \times 0.7 = 0.902$ ). We assume that the baseline 10-year DFS without regional node irradiation,  $p1$ , was 71.6% (weighted mean of trials) and calculated the expected DFS for the realized target coverage,  $p2 = p1^{HReffective}$ . Finally, the EAR was evaluated as the absolute loss comparing with the “ideal” HR = 0.86:  $EAR = p1^{HR} - p1^{HReffective}$ . Mean IMN doses >50 Gy were truncated at 50 Gy in the modeling (4 photon and 3 proton plans).

## Results

Patient characteristics are provided in Table 1. An illustrative example of the comparative treatment plans is presented in Figure 1.

**Table 1** Characteristics of 41 patients receiving radiation therapy at Rigshospitalet during 2015

	Data
Age, median (range), y	53 (26-79)
Tumor category, n	
T1 (<20 mm)	24 (59%)
T2 (20-50 mm)	15 (37%)
T3 (>50 mm)	2 (5%)
Cancer stage, n	
I	10 (24%)
II	20 (49%)
III	9 (22%)
Unknown	2 (5%)
No. of positive nodes, n	
0	2 (5%)
1-3	28 (68%)
4-9	6 (15%)
>9	4 (10%)
Unknown	1 (2%)
HER2 status, n	
Positive	7 (17%)
Negative	34 (83%)
ER status, n	
Positive	37 (90%)
Negative	4 (10%)
Adjuvant treatment, n	
None	1 (2%)
Chemotherapy*	29 (71%)
Trastuzumab	6 (15%)
Hormone therapy†	36 (88%)
No. of intercostal spaces in IMN target,‡ n	
2	1 (2%)
3	17 (41%)
4	21 (51%)
5	2 (5%)

Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; IMN = internal mammary node.

\* All received a combination of epirubicin, cyclophosphamide, and docetaxel. Three patients received neoadjuvant chemotherapy.

† Nineteen patients received letrozole, and 17 received tamoxifen.

‡ Department guidelines recommend 3 intercostal spaces (IMN delineated to cranial border of fourth rib). Four intercostal spaces are recommended in cases with medial tumor location.

Proton treatment planning provided more homogeneous target coverage and sparing of dose to heart, LADCA, and ipsilateral lung compared with the delivered photon plans in all 41 patients. The median target coverage HI was 0.13 (range, 0.07-0.7) for photon plans and 0.05 (range, 0.04-0.07) for protons. Figure 2A shows mean doses to delineated structures with the 2 radiation treatment modalities; despite a varying degree of underdosage of the IMN with photon therapy, the MHD was lower with protons. Figure 2B shows MHD and mean IMN dose. The median MHD was 1.9 Gy (range, 0.5-7.6 Gy) with photon planning and 0.3 Gy (range, 0.04-0.9 Gy) with proton planning. The 2 patients receiving the highest MHDs with photons, 7.6 and 6.6 Gy, respectively, were treated with the hybrid photon technique. The median mean IMN dose was 48.5 Gy (range, 37.1-50.7 Gy) with photons and 49.7 Gy (range, 49.0-50.1 Gy) with protons.

## Bioeffect modeling

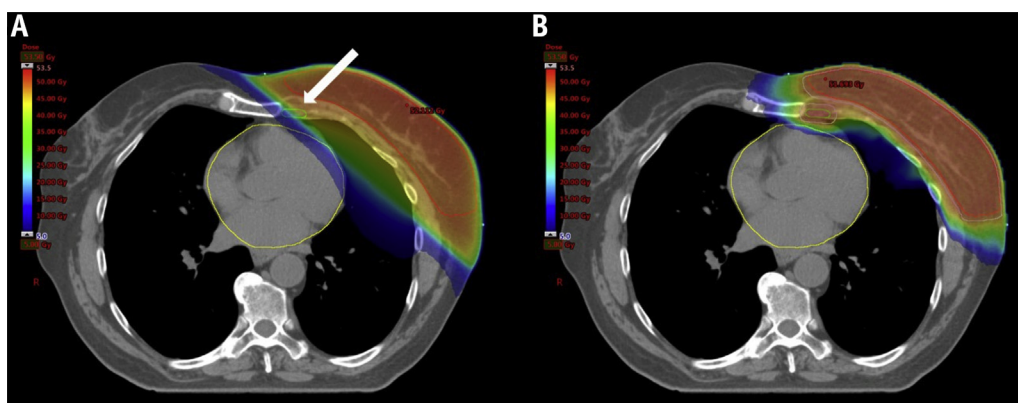
All patients had a lower EAR of at least 1 ACE at age 80 years with the proton treatment planning (Fig. 3). With no pre-existing CRFs, the median EAR for the photon plans was 0.5% (range, 0.03%-1.0%), and in the presence of CRFs, it was 1.0% (range, 0.2%-2.9%). In the proton case, the median EAR of at least 1 ACE by age 80 years was 0.06% (range, 0.004%-0.3%) and 0.13% (range, 0.02%-0.5%) without CRFs and with CRFs, respectively. The error bars in Figure 3 document the robustness of photon and proton plans and suggest that photon plans were often at least as sensitive to setup errors as proton plans. Figure A2 (available online at [www.redjournal.org](http://www.redjournal.org)) presents additional information.

The estimated EARs of breast cancer recurrence after 10 years using the model based on mean dose to IMN were essentially 0% for all proton plans and in the range of 0% to 0.9% (median, 0.10%) with photon planning (Fig. 4). A sensitivity analysis of the effect of model assumptions is presented in Appendix (available online at [www.redjournal.org](http://www.redjournal.org)).

## Discussion

Modern photon radiation therapy lowers the MHD (14) compared with historical cohorts. The delivered photon plans in this study of comprehensive nodal irradiation of left-sided breast cancer had a median MHD of 1.9 Gy, which is lower than that in most previous reports and the expected MHD of the RADCOMP (Radiotherapy Comparative Effectiveness) trial comparing photon and proton irradiation. However, although cardiac dose has decreased over time, it is not a solved problem. Patients in this series still had MHDs of up to 7.6 Gy. At the same time, IMN doses were as low as 37 Gy, indicating a substantial compromise to spare the heart, which may again cause a clinically relevant risk of recurrence (3).



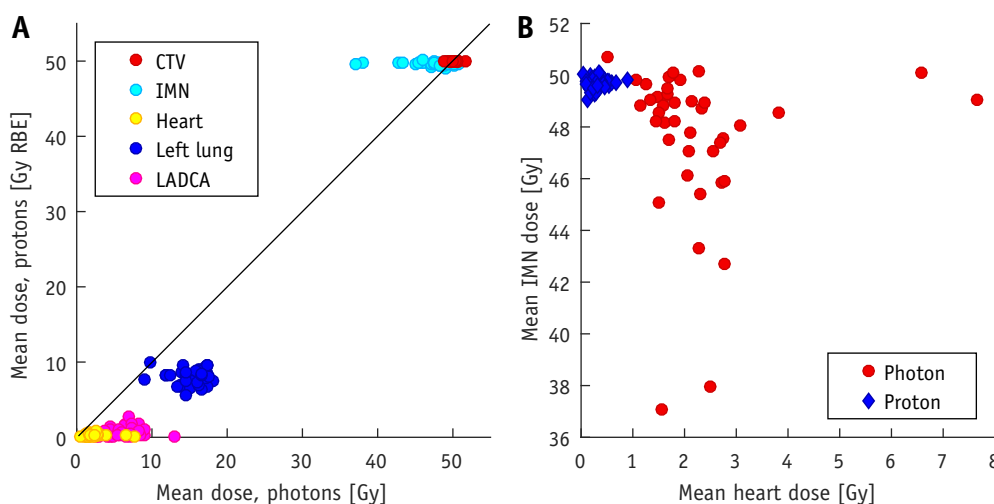


**Fig. 1.** The photon plan delivered to a patient at Rigshospitalet in 2015 (A) and the comparative proton plan (B). Both dose washes show the 10% to 107% dose range, and the computed tomography scan is obtained in deep inspiration breath hold. One should note the underdosage of the internal mammary node (white arrow) in the photon plan required to comply with the protocolized maximum dose to the heart (yellow structure). On the comparative proton plan, the internal mammary node is adequately dosed at the same time as the heart is spared more than with photons. The light purple structure on the proton plan is the proton-specific planning target volume.

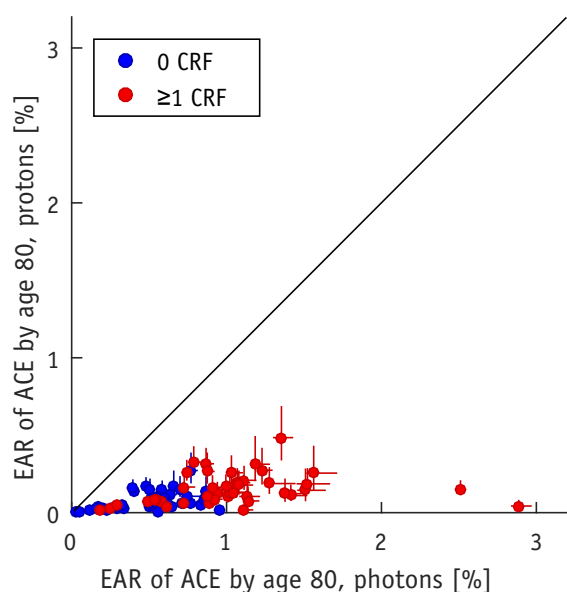
We used clinically delivered photon plans for comparison with protons in a comparatively large patient series to elucidate the distribution of potential benefit across a population. Clearly the predicted benefit of protons will depend on the target delineations and will likely be larger if the IMN delineations are expanded compared with the clinical plans (cf Table 1). Also, it should be noted that our primary target includes only breast tissue in a tighter definition than depicted in the delineation guidelines for the

RADCOMP trial, which may lead to conservative estimation of the amount of benefit from protons. In addition, it should be expected that the dose plans in the randomized trials do not cover the entire IMN as assumed here, and it may thus be speculated that a gain exceeding  $HR = 0.86$  is possible with protons.

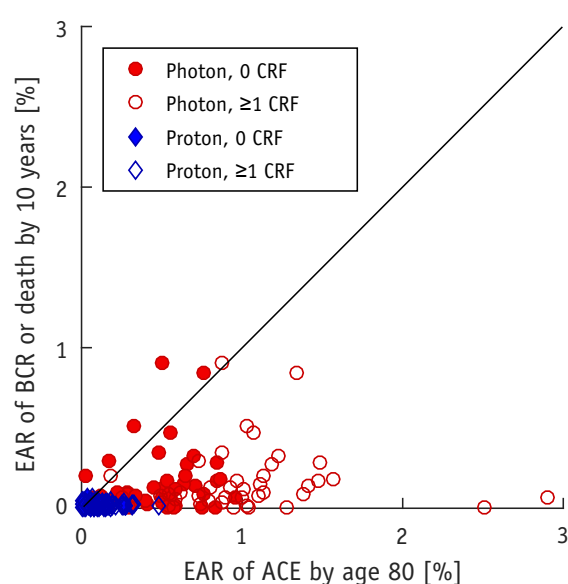
Compared with previous studies, our approach is novel by simultaneously considering the target coverage and risk of toxicity in the outcome estimation (15). The MHD or



**Fig. 2.** (A) Mean doses for various delineated structures using the delivered photon plan (x-axis) and the comparative proton plan (y-axis) for all 41 patients. Organs at risk (heart, left anterior descending coronary artery [LADCA], and left lung) below the line of identity are spared with protons. The internal mammary node (IMN) should ideally receive  $\geq 45$  Gy but is sometimes compromised to avoid overdosing the heart. One should note that the IMN is included in the clinical target volume (CTV). RBE = relative biological effectiveness. (B) Dosimetric quantification of target coverage versus cardiac dose compromise for all 41 patients, with the mean IMN dose on the y-axis versus mean heart dose on the x-axis. The red circles are the delivered photon plans, and the blue diamonds are the comparative proton plans (relative biological effectiveness corrected). (A color version of this figure is available at [www.redjournal.org](http://www.redjournal.org).)



**Fig. 3.** Excess absolute risk (EAR) of at least 1 acute coronary event (ACE) by the age of 80 years, modeled according to the study of Darby et al (4), for the comparative proton plans (y-axis) versus the clinically delivered photon plans (x-axis) in the 41 patients. The patients' age at irradiation is the actual age, whereas all patient cases are modeled without cardiac risk factors (CRFs, blue circles) and with at least 1 CRF (red circles). Symbols below the identity line indicate dosimetric superiority of the proton plan in terms of heart sparing. Error bars represent the result of the robustness analysis, that is, the 95% confidence interval of the risks as a consequence of setup uncertainties and stopping power conversion errors as described in detail in Appendix (available online at [www.redjournal.org](http://www.redjournal.org)). One should note that photon plans are often at least as sensitive as protons, as well as that the 2 patients with  $\text{EAR} > 2\%$  for photon treatment and at least 1 CRF are 70 years old. (A color version of this figure is available at [www.redjournal.org](http://www.redjournal.org).)

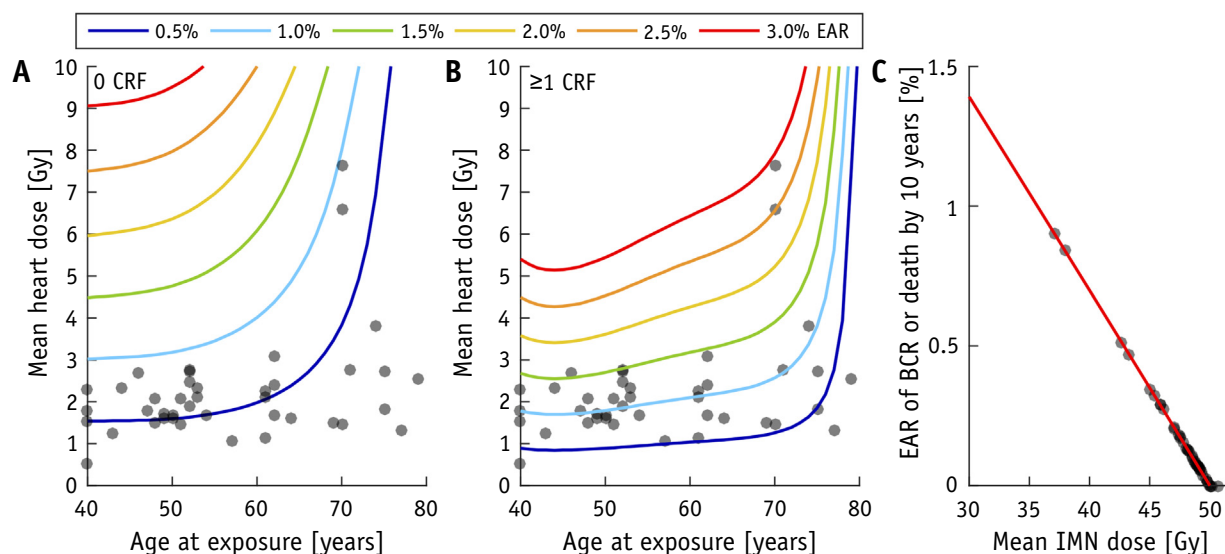


**Fig. 4.** Excess absolute risk (EAR) of breast cancer recurrence (BCR) within 10 years of therapy as compared with expected risk with mean dose to internal mammary nodes equal to prescribed dose (y-axis) versus EAR of at least 1 acute coronary event (ACE) at age 80 years resulting from cardiac irradiation (x-axis). Red symbols are the delivered photon plans, and blue symbols are the comparative proton plans. Filled symbols represent no pre-existing cardiac risk factors (CRFs), and open symbols represent at least 1 pre-existing CRF. Details about the recurrence and heart toxicity models are available in the text. (A color version of this figure is available at [www.redjournal.org](http://www.redjournal.org).)

mean IMN dose versus patient age and associated risk of ACE and breast cancer recurrence or death are depicted in Figure 5, along with the results of our 41 patients. Such risk assessments can provide clinical decision support regarding the potential benefits of proton therapy in an individual. It is interesting that modern proton beam spot scanning techniques can reduce both excess risks to essentially zero, thus eliminating the need for comparative dose planning in the decision process. In addition, it should be noted that the benefit from proton therapy across the 41 patients studied here does not correlate well with patient age (one should also refer to Fig. A3; available online at [www.redjournal.org](http://www.redjournal.org)). We, therefore, conclude that age is an inappropriate criterion for referral of breast cancer patients for proton therapy. Instead, we suggest that the MHD and the amount of compromise on IMN coverage are considered individually for each patient, as

possibly supported by Figure 5. Patients with unacceptable heart doses or compromises to IMNs could then be considered for proton therapy. We refrain from recommending a fixed threshold given the uncertainty of the models, but we recommend that possible cost-effectiveness analyses in the future also consider the possible loss of tumor control from compromising the target, rather than cardiac dose alone (16).

A number of limitations of this study should be acknowledged. First, the bioeffect modeling is associated with substantial uncertainty, especially the models of risk of recurrence. Model uncertainties and a sensitivity analysis using another dose metric to predict risk of breast cancer recurrence are presented in Figures A4 and A5 in Appendix (available online at [www.redjournal.org](http://www.redjournal.org)). Clearly the results are uncertain, but our present attempt gives a realistic scale of the issue and is, to our knowledge, the first outcome data-driven model of breast cancer recurrence resulting from target compromises. With respect to cardiac risk estimates, there are a number of modeling assumptions discussed in the communications on the article by Darby et al (4). In addition, the use of anthracycline and taxanes was infrequent in the study of Darby et al but may possibly amplify the effect of cardiac irradiation.



**Fig. 5.** Excess absolute risk (EAR) contours of at least 1 acute coronary event (ACE) by age 80 years without (A) and with cardiac risk factors (CRFs) (B) as a function of age at exposure (x-axis) and mean heart dose (MHD) (y-axis) from the photon plan. (C) EAR of breast cancer recurrence (BCR) by 10 years after therapy as a function of mean dose to internal mammary nodes (IMNs). The gray symbols in A, B, and C represent the age-dose data from the 41 patients.

All plans were modeled on a DIBH CT scan, which can only be delivered in the newest proton therapy centers and, to our knowledge, has not been introduced clinically (17-19). Nevertheless, filling the lung with air has little effect on cardiac dose for proton therapy (20) with en face beam arrangement as the beam range depends predominantly on radiologic and not geometric distance (ie, the mass of tissue in the beam path rather than the length of the beam path). Also, our results apply to installations with spot scanning capabilities. On the other hand, the presented results reflect advanced photon plans in DIBH, and centers without access to such techniques may see a larger proportion of patients benefitting from proton therapy referrals. Again, we recommend using the dose-risk comparisons (eg, Fig. 5) as support for clinical decisions rather than standardizing referral guidelines based on, for example, patient age.

In conclusion, a method has been demonstrated to estimate the joint risk of breast cancer recurrence and cardiac morbidity following compromises to target coverage and radiation exposure to the heart, respectively. Modern photon techniques, specifically delivery in DIBH, are associated with a low predicted risk of cardiotoxicity; however, a subset of patients may still have a relevant benefit from referral to proton therapy. Joint estimation of breast cancer recurrence and cardiac morbidity risk should be considered as an integral component of clinical decision support and for shared decision making with prospective patients, albeit with acknowledgment of the uncertainties of the modeling.

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